REMARKS

Claims 1-13 are pending in the subject application.

Claims 1-3 and 6-13 are drawn to the elected species and examined on the merit. Claims 1-11 are generic as indicated in the Examiner's Action dated May 9, 2007.

Applicants request favorable reconsideration in view of the following remarks.

Claim Rejections - 35 U.S.C. §103

The Examiner's Action rejected claims 1-3 and 6-13 as being unpatentable over Hu et al., Biotechnology Letters, 24, 275-278, 2002 (Hu article), in view of Bonhard et al., U.S. Patent No. 4,336,248 (Bonhard Patent), further in view of known hemoglobin (protein) purification methods.

In response, Applicants submit that the present invention as set forth in claim 1 is not obvious over the cited prior art, and the Examiner's Action fails to establish a *prima facie* case of obviousness.

First, there is no motivation to combine the Hu article with the Bonhard Patent. The Hu article discloses a conjugate of bovine serum albumin and bovine hemoglobin. See Abstract. As disclosed at column 1, second paragraph, to column 2, first full paragraph, at page 275, the Hu article discusses the difficulty of using dialdehyde as the crosslinker between the hemoglobin and serum albumin and provides an alternative to using dialdehyde in the Hu article:

> Interestingly, hemoglobin has been coupled with serum albumin using dialdehyde, a homobifunctional reagent, to increase its half-life time . . . However, heterogeneous products were formed in the crosslinking process. As a result, it is difficult to determine the consistency of the coupled hemoglobin. ...Alternatively, a bovine serum albumin (BSA) - bovine hemoglobin conjugate can be prepared as is described in this present paper.

The Hu article points out the disadvantage of using dialdehyde as the crosslinker and refrains from using it. Moreover, at column 2, first paragraph, on page 275, the Hu article discloses that it uses bovine hemoglobin because it "does not appear to cause rapid antibody formation when injected into non-bovine species" and thus, attempts to "use bovine hemoglobin as a substitute for human blood."

The Bonhard Patent discloses "coupling hemoglobin molecules to one another and/or to serum proteins and gelatin derivatives using dialdehydes such as aliphatic dialdehydes of 3 to 8 carbon atoms." See abstract. The Bonhard Patent uses dialdehydes for coupling of hemoglobin molecules. Column 1, lines 29-40 and 63; In all the 16 Examples in the Bonhard Patent, dialdehydes are used for coupling in each and every example.

Based on the teachings of the Hu article, which refrains from using a dialdehyde as the crosslinker and provides an alternative, and the Bonhard Patent, which requires the use of dialdehyde in the coupling of hemoglobin, one of ordinary skilled in the art would not combine the two references.

As discussed in the Bonhard Patent, coupling hemoglobin with other molecules increases the oxygen carriers size, so that it achieves a longer residence time of the molecular transporting oxygen for a longer-lasting intravascular effect than a single hemoglobin molecule. Since the protein conjugates in the Hu article and the Bonhard Patent are different, one of ordinary skilled in the art would not be motivated and combined the teachings of the two. Therefore, there is no motivation to combine these two references.

Second, even if the Hu article is combined with the Bonhard patent, they still fail to teach the present invention as set forth in claim 1.

The Hu article uses bovine hemoglobin for its low immunogenicity. There is no indication that human hemoglobin would have the same property or can be used in the conjugate of the Hu article. As admitted in the Examiner's Action at page 3, line 3, the Hu article "do not make or use an albumin/hemoglobin conjugate of human origin." Such a missing teaching in the Hu article is not supplied by the Bonhard Patent. The Bonhard Patent does not teach the use of serum albumin of human origin.

Careful study of Examples 6-7 and 11-12 of the Bonhard Patent reveals that none of these Examples teach serum albumin or hemoglobin of human origin. Examples 6 and 7 disclose that the coupling product was obtained by using hemoglobin and serum albumin, not human serum albumin. Examples 11 and 12 disclose the use of hemoglobin solution and "human serum containing 5% of protein." The Examples clearly indicate that it is human serum, not human serum albumin, that is used. The Examiner's Action fails to give a reason why, to one of ordinary skill in the art, human serum containing 5% of protein includes human serum albumin.

Neither the Hu article nor the Bonhard Patent disclose the conjugate of human hemoglobin and human serum albumin. Applicants disagree with the Examiner's assertion that one of ordinary skill in the art "has a reasonable expectations of success in preparing and using such HSA/hHb product because the structures of bovine and human hemoglobin and albumin are very similar and one of ordinary skill at first glance, expects to use the same ratio of said bovine proteins for preparation of human HAS/hHb conjugates" and thus, renders the invention obvious. The Examiner fails to

define the level of ordinary skill in the art. Applicants request that the Examiner clarify as to what constitutes the level of ordinary skill in the art under the established law. Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966); KSR International v. Teleflex, 550 U.S., 82 USPQ.2d 1385 (2007); Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc., Federal Register, Vol. 72, No. 195, 57527 (October 10, 2007).

Further, to a person of ordinary skill in the art of immunology and hematology, the Examiner's Action fails to provide any reasonable expectation of success as to the advantage of Ha-ha conjugate. In Immunology, structural similarity of the antigens does not warrant similar immune response, and even much less so for a conjugate after the linking of the two proteins. Voluminous patents and research articles on the modification of the hemoglobin to reduce its immunogenicity are the testaments to the error in the Examiner's assertion. Absence of any evidence, the Examiner's Action fails to establish a *prima facie* case of obviousness.

Third, the present invention shows unexpected result which would rebut any obviousness over the cited prior art.

The present invention provides a hemoglobin-contained blood substitute having low immunogenicity in different kinds of mammals. As shown in Examples 12 and 13 of the specification, the conjugates of the present invention achieve unexpected results of low immunogenicity and toxicity and work as substitute for the whole blood.

In conclusion, there is no *prima facie* case of obviousness. Particularly, there is no motivation to combine the Hu article with the Bonhard patent, and even if they are

combined, they still fail to teach the present invention. Moreover, the present invention shows unexpected results which would rebut any obviousness over the prior art. Therefore, the present invention as set forth in claim 1 is not obvious over the cited prior art. Since claims 2-13 depend on claim 1, they are also patentable over the cited prior art.

In view of the foregoing, all rejections have been overcome and all claims 1-13 are in condition for allowance, early notice of which is requested.

No fee is believed to be due for this response. Should any fees be required, please charge the same to Deposit Account No. 50-2586 and notify Applicants' attorney.

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Respectfully submitted,

PERKINS COIE LLP

By: _____
Manni Li
Registration No. 57,400

Correspondence Address
Customer No. 34055
Perkins Coie LLP
Patent - LA
P.O. Box 1208
Seattle, WA 98111-1208
Phone: (310) 788-9900
Fax: (206) 332-7198